



# Ethics of clinical research

Olivier Jonquet



Raphaël *L'Ecole d'Athènes* (1510)



# Aristote (384-322 BC)

- *Virtue is not natural, but is not against nature* (NE, 1103a24)
- *Life is contingency: vita in motu*
- Prudence is a cardinal virtue ; has its origin in reason
- Realistic moral : art of possible
  - to keep within bounds
  - prudence
  - self developpement



*What can I know?*

*What ought I to do?*

*What may I hope?*

Immanuel Kant (1724-1804)

# Kant : categorical imperative

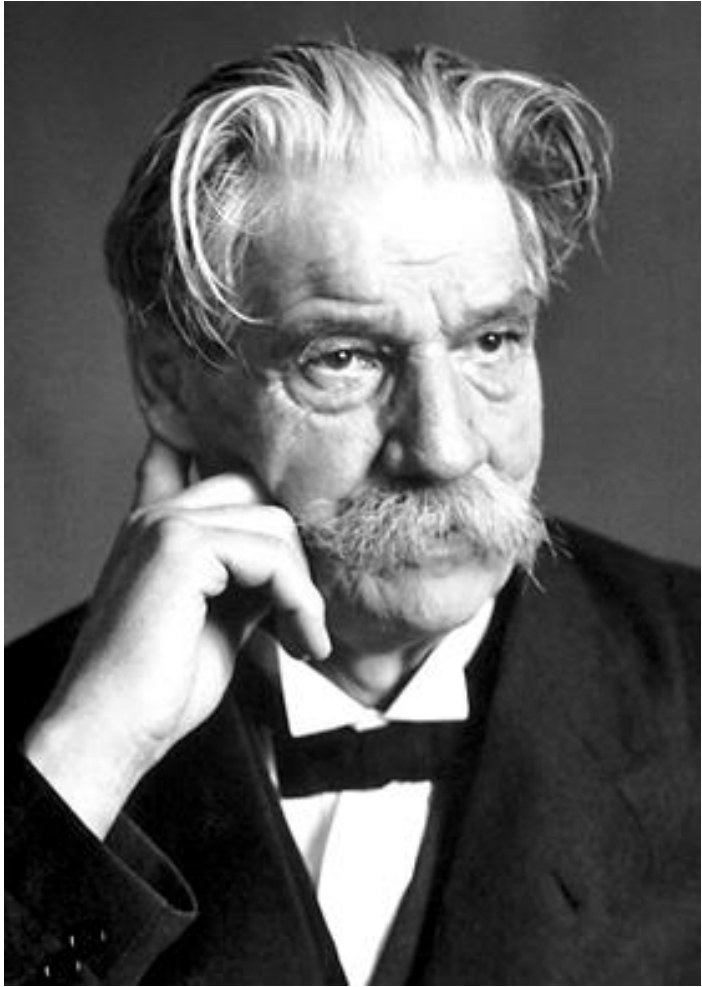
- 1-*Act only according to that maxim whereby you can at the same time will that it **should become a universal law without contradiction***
- 2-*Act in such a way that **you treat humanity**, whether in your own person or any other, never merely as a means to an end, but **always at the same time as an end**.*
- 3-*Thus the third practical principle follows as the ultimate condition of their harmony with practical reason : the idea of the very rational being as a **universally legislating will***

Groundings of the Metaphysics of Morals

# Paul Ricoeur (1913-2005)

- *The project of an accomplished life*
- *The goal of a good life with and for others within just institutions*
- *The shared admission of fragility*
- Inevitability of moral conflict (*Antigone-Creon*)  
*Antigon is as inhuman as Creon*
- *Dialogic dimension* : concrete wisdom that applies abstract rules to concrete cases and adapt moral and legal rules to concrete human needs and to the multiplicity of moral dilemmas

Jürgen Habermas (1929-), Emmanuel Levinas (1906-1995),  
John Rawls (1921-2002)...



*Ethics is  
recognition of our  
responsability  
towards anything  
living*

Albert Schweitzer (1875-1965)

**Mt 7,12**

*So in everything, do to others what you would have them do to you.*

**Lc 6,31**

*Do to others as you would have them do to you.*

**Rm 13,10**

*Love does no harm to a neighbor. Therefore love is the fulfillment of the law.*



Fritz Jahr (1895-1963)  
Pasteur luthérien allemand

Francis of Assisi

Jean-Jacques Rousseau

***Bio-Ethyk ; eine Umschau über die ethischen Beziehungen des Menschen zu Tier und pflanze***

*Bioéthique : a review of ethics relationships between men, animals and plants*

***Kosmos : Handweiser für Naturfreunde, 1927 24(1):2-4***

Science , research

# Methodologic groundings of science

- Science : *scire*
- Search objectivity, eliminate subjectivity
- Segmentation of the problem in sub independant problems
- No interaction between observer and observed
- Reproduction of results :

*Particular facts are never scientific; only generalization can establish science* (Claude Bernard)

- Invariability
- A cause, an effect
- Build models of the explored reality
- Know the HOW of the world, not WHY
- Morally neutral

# Why clinical research?

- Improve knowledge
  - on a disease (physiopathology, aetiology...)
  - on man

Improve treatments

- drugs
- devices
- ...

# Research on man (or woman...)

- Research activity with the goal to product a generalisable knowledge
  - activity : procedure, methodology
  - knowledge : distinct from care
  - generalisable, universal : from singular to general and from general to singular

Théophraste Bombast von Hohenheimdit : Paracelse (1493-1541)

*alterius non sit qui suus esse potest*



Medicine

- of the man
- of the human being
- of one man



**Claude Bernard (1813-1878)**

*Among the experiments that may be tried on man, those that can only harm are **forbidden**, those that are innocent are **permissible**, and those that may do good are **obligatory**.*

*It is **immoral** then, to make an experiment on man **when it is dangerous to him**, even though the result may be useful to others.*

*There are some doctors who declare themselves against **experimentation**, and only in favour **observation**. (...) experimentation cannot exist without observation. **Experiment is only provoked observation**.*

*Every day physician make therapeutic experiments on patients and every day surgeon do vivisections...*

# Hippocratic aphorisms

- Ὁ βίος βραχύς, Life is short
- ἡ δὲ τέχνη μακρὴ, Art is long
- ὁ δὲ καιρὸς ὀξύς, Opportunity fleeting
- ἡ δὲ πεῖρα σφαλερὴ, Experience perilous
- ἡ δὲ κρίσις χαλεπὴ Decision difficult

**SHOCK!!!**

# Courrier Adolf Hitler



BERLIN, 1. Sept. 1939.

Adolf HITLER

Berlin le 1<sup>er</sup> septembre 1939

Monsieur le directeur d'empire BAULHER et  
Monsieur le docteur en médecine BRANDT

Reichsleiter Baulher und  
Dr. med. Brandt

sind unter Verantwortung beauftragt, die Befugnisse namentlich zu bestimmender Ärzte so zu erweitern, dass nach menschlichem Ermessen unheilbar Kranken bei kritischster Beurteilung ihres Krankheitszustandes der Gnadentod gewährt werden kann.

Signé Adolf HITLER

mention manuscrite : apparemment

m'a été remis par Baulher le 27/8/1940

Signé : Dr Gütner

*Der Baulher mein  
über dem am 27.8.40  
Dr. Gütner*

Gnadentod : mort gracieuse  
Gnadenschuss : coup de grâce du fusillé

.....

# Nuremberg trial 18/10/1945-1/10/1946



# Nazi physicians trial Nuremberg 9/12/1946-21/08/1946





Dr Berthold Ostertag (1895-1975) Hôpital de la Charité Berlin



**Hypothermia experiment Dachau : Dr Sigmund Rascher et Dr Ernst Holzloehner**

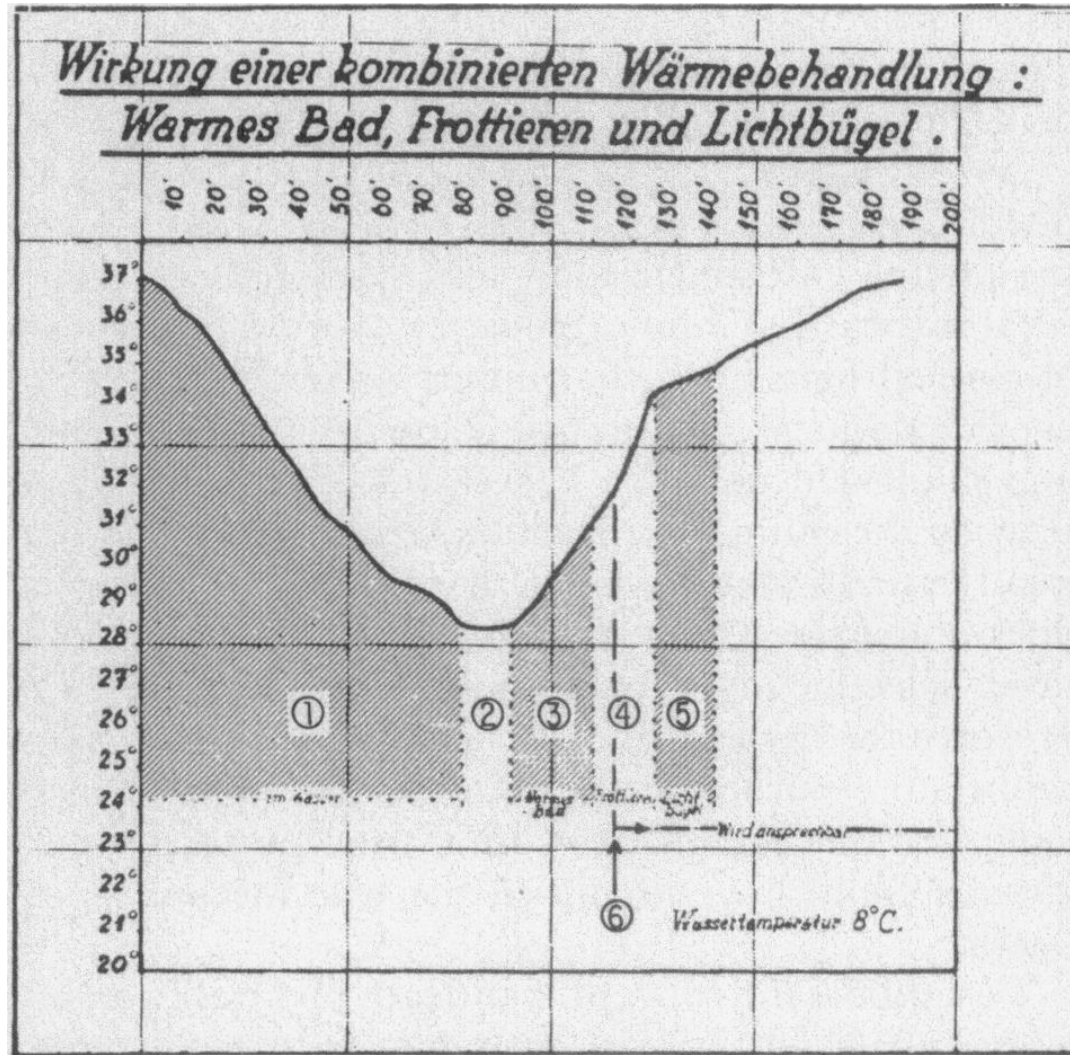
# SPECIAL ARTICLE

## NAZI SCIENCE — THE DACHAU HYPOTHERMIA EXPERIMENTS

ROBERT L. BERGER, M.D.

THE NEW ENGLAND JOURNAL OF MEDICINE

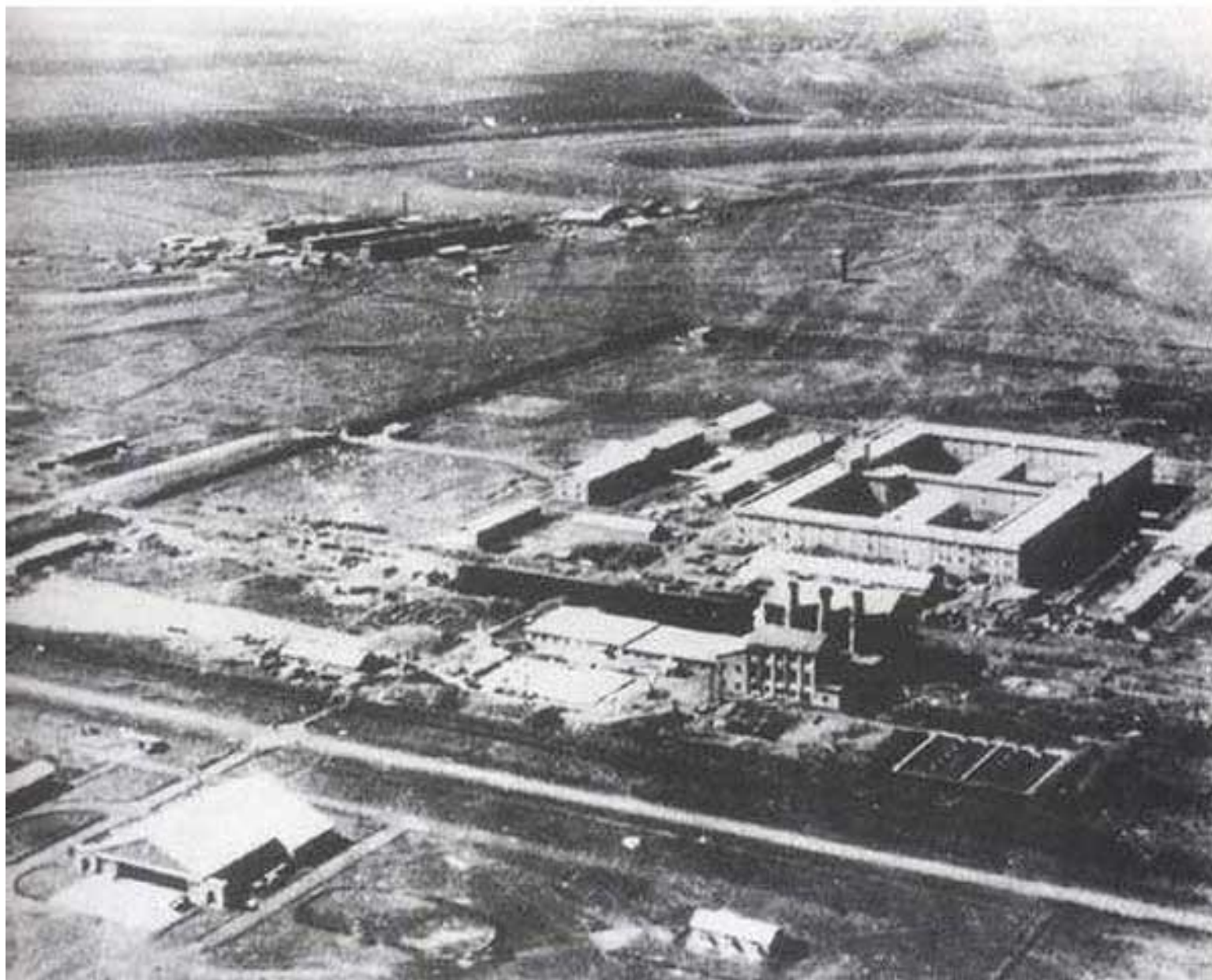
May 17, 1990



# Miscellaneous

- Paludism
- Typhus
- Tuberculosis
- Sterilizations
- Poisons
- « Polygal » : hemostatic
- Gas gangrene

Don't forget japanese!



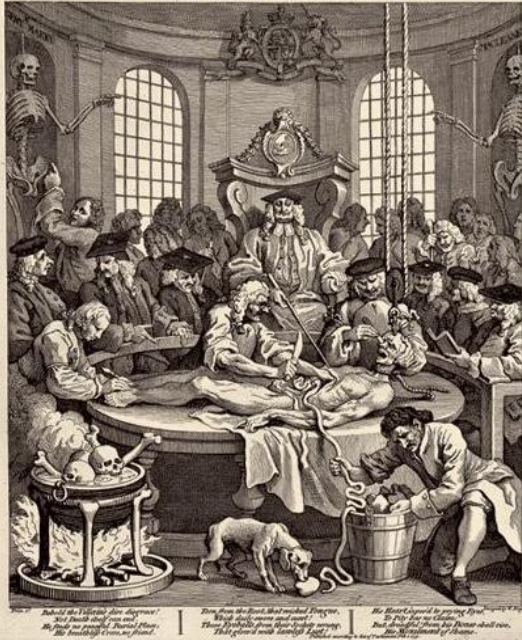
**Unité 731 Pengfan (Mandchourie)**



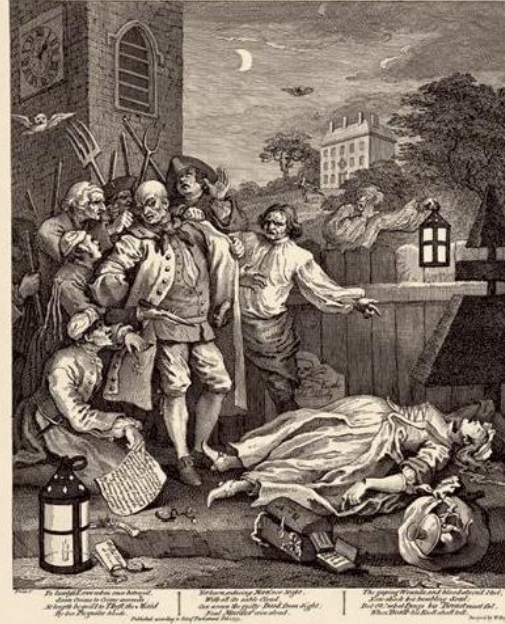
**Shiro Ishii (1892-1959)**

We come from far away

THE REWARD OF CRUELTY.



CRUELTY IN PERFECTION.



William Hogarth (1697-1764)

SECOND STAGE OF CRUELTY.



FIRST STAGE OF CRUELTY.



*For the custom of tormenting  
and killing of beasts will, by  
degrees, harden their minds  
even towards men.*

Locke (1632-1704)

Consent

Convicts  
*in corpore vili*

# Vivisections



- Hérophile (320-260 BC)

*Fiat experimentum in corpore vili*

*Herophilus, ille medicus aut lanius* (Celse)

- Diderot (1713-1784)

*Is guilty dissection inhuman?*



**The archer of Meudon : first surgical lithotomy Germain Colot in front of Louis XI (1474)**

# History

- Trial *Slater v. Baker-Stapelton*

*It appears from the evidence of the surgeons that it was improper to desunite the callous without consent ; this is the usage and law of surgeons*

- Coley's toxins

*After some deliberations, he consented*



WB Coley (1862-1936)

# History

- Louis Pasteur (1822-1895) *Lettre à l'empereur du Brésil*

- Sanarelli (1864-1940)

1897 five patients experiment injection of « bacillus » of yellow fever

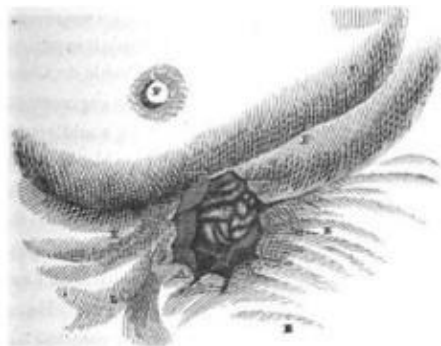
- William Osler (1849-1919)

*To deliberately inject a poison of known high degree of virulency into an human being, unless you obtain that man's sanction, is not ridiculous, it is criminal (1898)*



Alexis St. Martin at the age of 81 years. (From a photograph presented to Mr. William Osler.)

## Alexis Saint Vincent (1794-1880)



The appearance which is presented when the valve was pushed back is shewn in the above figure.

AAA, are the edges of the aperture. B indicates the cavity of the stomach as seen when the valve is depressed. C, the valve itself. EEE, the cicatrix of the original wound. F, the nipple.

*Showing the mean time of digestion of the different Articles of Diet, naturally, in the Stomach, and artificially, in Vials, on a bath.*

The proportion of gastric juice to aliment, in artificial digestion, was generally calculated at one ounce of the former to one drachm of the latter, the bath being kept as near as practicable at the natural temperature, 100° Fahrenheit, with frequent agitation.

Articles of Diet.	Mean time of chymification			
	In Stomach.		In Vials.	
	prep.	h. m.	prep.	h. m.
Rice, -	boiled	1 00		
Sago, -	do.	1 45	boiled	3 15
Tapioca, -	do.	2 00	do.	3 20
Barley, -	do.	2 00		
Milk, -	do.	2 00	do.	4 15
Do. -	raw	2 15	raw	4 45
Gelatine. -	boiled	2 30	boiled	4 45
Pig's feet, soured,	do.	1 00		
Tripe, do.	do.	1 00		
Brains, animal,	do.	1 45	do.	4 30
Venison, steak,	broiled	1 35		
Spinal marrow, animal,	boiled	2 40	do.	5 25
Turkey, domesticated,	roasted	2 30		
Do. do.	boiled	2 25		
Do. wild,	roasted	2 18		
Goose, do.	do.	2 30		
Pig, sucking -	do.	2 30		
Liver, beef's, fresh,	broiled	2 00	cut fine	6 30
Lamb, fresh,	do.	2 30		
Chicken, full grown,	fricas'd	2 45		
Eggs, fresh,	h'rd bld	3 30	h'rd bld	8 00
Do. do.	soft bld	3 00	soft bld	6 30
Do. do.	fried	3 30		
Do. do.	roasted	2 15		
Do. do.	raw	2 00	raw	4 15
Do. whipped.	do.	1 30	whipped	4 00
Custard, -	baked	2 45	baked	6 30
Codfish, cured dry,	boiled	2 00	boiled	5 00

# Walter Reed (1901)

- Ethics of research requires
  - self-experiment
  - written consent
  - remuneration, payment
  - only adult
  - mention in papers *with his full consent*



Figure 1.2. Walter Reed, standing in white uniform with colleagues, as Jesse Lazear inoculates James Carroll

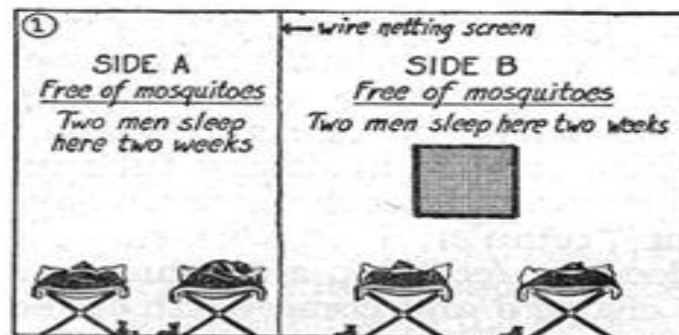
**Carlos Finlay (1833-1915)**

**Walter Reed (1851-1902)**

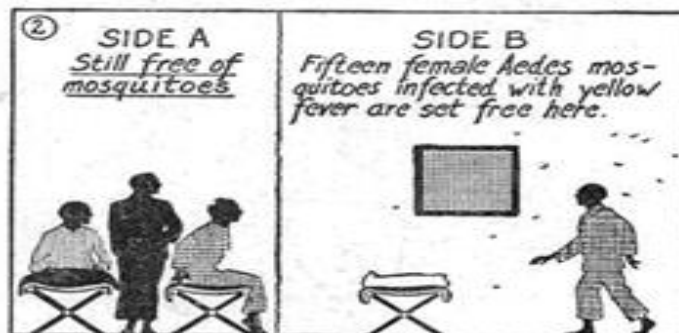
before mentioned - Thus:



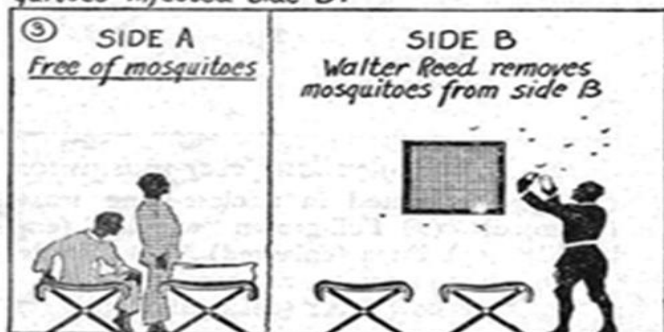
On the 21<sup>st</sup> at 11.35 am. we liberated 15 infected mosquitoes in the larger room, and at 11.55 am. a young american entered the room &



① All four men remain well. Therefore the building is not infected with yellow fever



② J. Moran enters side B, is bitten and has yellow fever in four days. The men in side A remain well. Therefore the presence of contaminated mosquitoes infected side B.



③ Men sleep on both sides of wire netting as before without taking yellow fever. Therefore side B has been disinfected by removing mosquitoes

**Figure 1.1.** Illustrated Depiction of Yellow Fever Experiment. Source: Papers of Jefferson Randolph Kean, MSS 628, Special Collections, University of Virginia Library, Charlottesville, Va. Reproduced with permission.



**Carlos Finlay (1833-1915)**

**Walter Reed (1851-1902)**



**Bonaparte**

## **Les pestiférés de Jaffa**



**Desgenettes**



Werner Forssman (1904-1979)  
First cardiac catheterism (with ureteric catheter)



Heart surgery evolved thanks to Werner Forssman. In 1929, he believed you could insert a catheter into the heart. People said he was crazy, so he put a catheter into his own heart to prove it. Even though it worked, he got fired. Then he became a Nazi, but still won the Nobel Prize... and then he died of heart failure.

# Consent

- *Agree with*
- From latin *consentire* : *feeling with*
- *Consensus* (Cicero 106-43 BC): in accordance with oneself, others and nature
- Implies a sympathy between two persons and not between a person and a project or a paper (of full consent...)
- Ethical involvement
- But is not sufficient (dwarf tossing)!

# Dignity : Immanuel kant

*What is related to general human inclinations and needs has a market price;*

*That which, even without presupposing such a need, conforms with a certain taste has a fancy price;*

*But that which constitutes the condition under which alone something **can be an end in itself has not merely a relative value, that is, a price, but an inner value, that is dignity.***

*Morality, and humanity insofar as it is capable of morality, is that which alone has dignity*

# Information

- Give a *form* to a *substance* (Aristote)
- Help patient to be shaped (*en forme*), in accepted way (dans les *formes*)



Michelangelo (1475-1564) *Pieta*

End of the second world war  
(1939-1945)

## Nazi physicians trial Nuremberg 9/12/1946-21/08/1946



# Nuremberg code

- 1-Required is the **voluntary, well-informed, understanding consent** of the human subject in a full legal capacity.
- 2-The experiment should **aim at positive results for society** that cannot be procured in some other way.
- 3-It should be based on **previous knowledge** (like, an expectation derived from animal experiments) that justifies the experiment.
- 4-The experiment should be set up **in a way that avoids unnecessary physical and mental suffering and injuries**.
- 5-It should **not be conducted** when there is any reason to believe that it implies **a risk of death or disabling injury**.

# Nuremberg code

- 6-The **risks** of the experiment should be **in proportion to** (that is, not exceed) the expected humanitarian benefits.
- 7-Preparations and facilities must be provided that adequately **protect the subjects against the experiment's risks.**
- 8-The **staff** who conduct or take part in the experiment **must be fully trained and scientifically qualified.**
- 9-The **human subjects must be free to** immediately **quit** the experiment at any point when they feel physically or mentally unable to go on.
- 10-Likewise, **the medical staff must stop** the experiment at any point **when they observe** that continuation would be **dangerous.**

**Special Communication**

# World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
- 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
- 59th WMA General Assembly, Seoul, Republic of Korea, October 2008
- 64th WMA General Assembly, Fortaleza, Brazil, October 2013

<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

All is right?

# Tuskege (Alabama)

- From 1932, forty years follow-up of 400 syphilitic black people and 200 free subjects
- Aim : understand natural course of the disease
- But : 1932 Salvarsan® (Paul Ehrlich Nobel prize 1908)  
1944 Penicillin
- 1969 CDC continues experiment
- 1972 investigations by newspapers...
- 1997 Pdt Clinton apologizes : *clearly racist study*...

# Willowbrook

- Center for mentally retarded children
- Children were intentionally given hepatitis in an attempt to track development of hepatitis
- Follow-up by NYC university
- They justified their deliberate infections and exposures by claiming that given that there was a high rate of infection in the institution it was practically inevitable that the children would become infected.
- Natural history of a disease...

*The Willowbrook Letters: Criticisms and Defense.* **The Lancet**, April 10, May 8, June 5, and July 10, 1971

- After, Belmont report

Belmont report : *Principles of bioethics*  
(Beauchamp and Childress 1978)

- **Autonomy** – one should respect the right of individuals to make their own decisions

**Nonmaleficence** – one should avoid causing harm

**Beneficence** – one should take positive steps to help others

**Justice** – benefits and risks should be fairly distributed

# In France

- Nothing until 1988...
- Huriet-Serusiclat Law defines conditions for ethical research

Developping countries?

# The New England Journal of Medicine

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## REDUCTION OF MATERNAL-INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

EDWARD M. CONNOR, M.D., RHODA S. SPERLING, M.D., RICHARD GELBER, PH.D., PAVEL KISELEV, PH.D.,

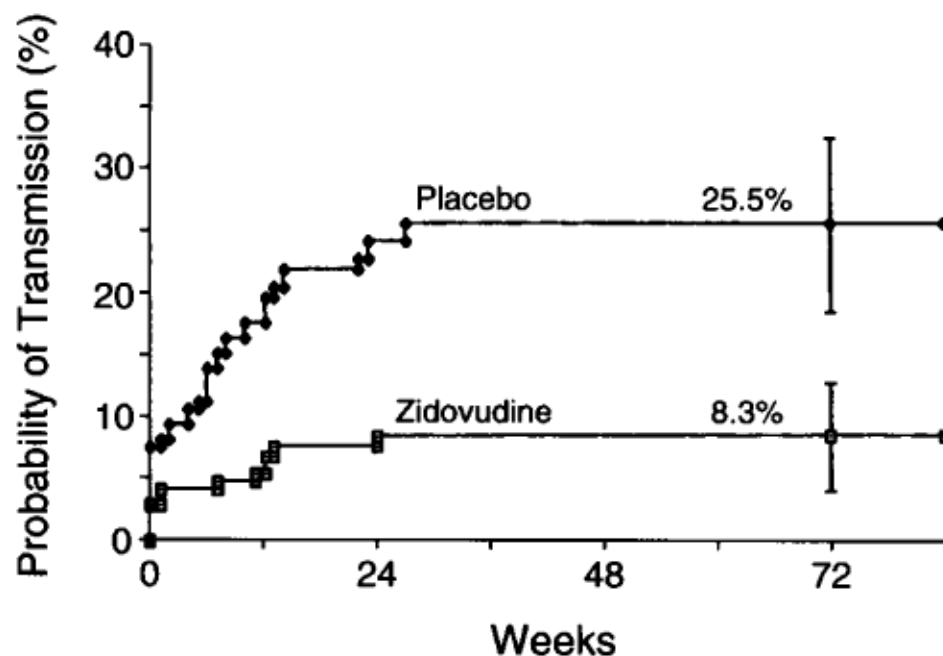
**Table 3. Alternative Efficacy Analyses.\***

VARIABLE	ZIDO- VUDINE	PLACEBO	ALL
<b>Infants &gt;32 wk</b>			
Births (no.)	150	149	299
Infection status (no.)			
Indeterminate	29	22	51
Defined	121	127	248
HIV-infected	9	31	40
Transmission rate (%)†	7.4	24.4	16.1
<b>Infants ≥1 yr</b>			
Births (no.)	95	104	199
Infection status (no.)			
Indeterminate	12	15	27
Defined	83	89	172
HIV-infected	7	20	27
Transmission rate (%)‡	8.4	22.5	15.7

\*In these analyses, two positive cultures define HIV infected, and at least two negative cultures (one obtained at ≥24 weeks) and no positive cultures define the absence of HIV infection. P values were determined with the chi-square test.

†P = 0.002 for the comparison between groups.

‡P = 0.03 for the comparison between groups.



Placebo	183	84	42	37
Zidovudine	180	105	51	43

# Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial

THE LANCET • Vol 353 • March 6, 1999

*Nathan Shaffer, Rutt Chuachoowong, Philip A Mock, Chaiporn Bhadrakom, Wimol Siriwasin, Nancy L Young, Tawee Chotpitayasunondh, Sanay Chearskul, Anuvat Roongpisuthipong, Pratharn Chinayon, John Karon, Timothy D Mastro, R J Simonds, on behalf of the Bangkok Collaborative Perinatal HIV Transmission Study Group*

**Methods** In a randomised, double-blind, placebo-controlled trial, HIV-1-infected pregnant women at two Bangkok hospitals were randomly assigned placebo or one zidovudine 300 mg tablet twice daily from 36 weeks' gestation and every 3 h from onset of labour until delivery. Mothers were given infant formula and asked not to breastfeed. The main endpoint was babies' HIV-1-infection status, tested with HIV-1-DNA PCR at birth, 2 months, and 6 months. We measured maternal plasma viral concentrations by RNA PCR.

**Findings** Between May, 1996, and December, 1997, 397 women were enrolled; 393 gave birth to 395 live-born babies. Median duration of antenatal treatment was 25 days, and median number of doses during labour was three. 99% of women took at least 90% of scheduled antenatal doses. Adverse events were similar in the study groups. Of 392 babies with at least one PCR test, 55 tested positive: 18 in the zidovudine group and 37 in the placebo group. The estimated transmission risks were 9.4% (95% CI 5.2–13.5) on zidovudine and 18.9% (13.2–24.2) on placebo ( $p=0.006$ ; efficacy 50% [15.4–70.6]). Between enrolment and delivery, women in the zidovudine group had a mean decrease in viral load of 0.56 log. About 80% of the treatment effect was explained by lowered maternal viral concentrations at delivery.

**Interpretation** A short course of twice-daily oral zidovudine was safe and well tolerated and, in the absence of breastfeeding, can lessen the risk for mother-to-child HIV-1 transmission by half. This regimen could prevent many HIV-1 infections during late pregnancy and labour in less-developed countries unable to implement the full 076 regimen.

*Lancet* 1999; **353**: 773–80

# Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial

Stefan Z Wiktor, Ehounou Ekpini, John M Karon, John Nkengasong, Chantal Maurice, Sibailly T Severin, Thierry H Roels, Moise K Kouassi, Eve M Lackritz, Issa-Malick Coulibaly, Alan E Greenberg

THE LANCET • Vol 353 • March 6, 1999

**Methods** From April, 1996, to February, 1998, all consenting, eligible HIV-1-seropositive pregnant women attending a public antenatal clinic in Abidjan were enrolled at 36 weeks' gestation and randomly assigned placebo or zidovudine (300 mg tablets), one tablet twice daily until the onset of labour, one tablet at onset of labour, and one tablet every 3 h until delivery. We used HIV-1-DNA PCR to test the infection status of babies at birth, 4 weeks, and 3 months. We stopped the study on Feb 18, 1998, when efficacy results were available from a study in Bangkok, Thailand, in which the same regimen was used in a non-breastfeeding population.

## Findings

breastfed. Among babies with known infection status at age 3 months, 30 (26·1%) of 115 babies in the placebo group and 19 (16·5%) of 115 in the zidovudine group were identified as HIV-1 infected. The estimated risk of HIV-1 transmission in the placebo and zidovudine groups were 21·7% and 12·2% ( $p=0·05$ ) at 4 weeks, and 24·9% and 15·7% ( $p=0·07$ ) at 3 months. Efficacy was 44% (95% CI -1 to 69) at age 4 weeks and 37% (-5 to 63) at 3 months.

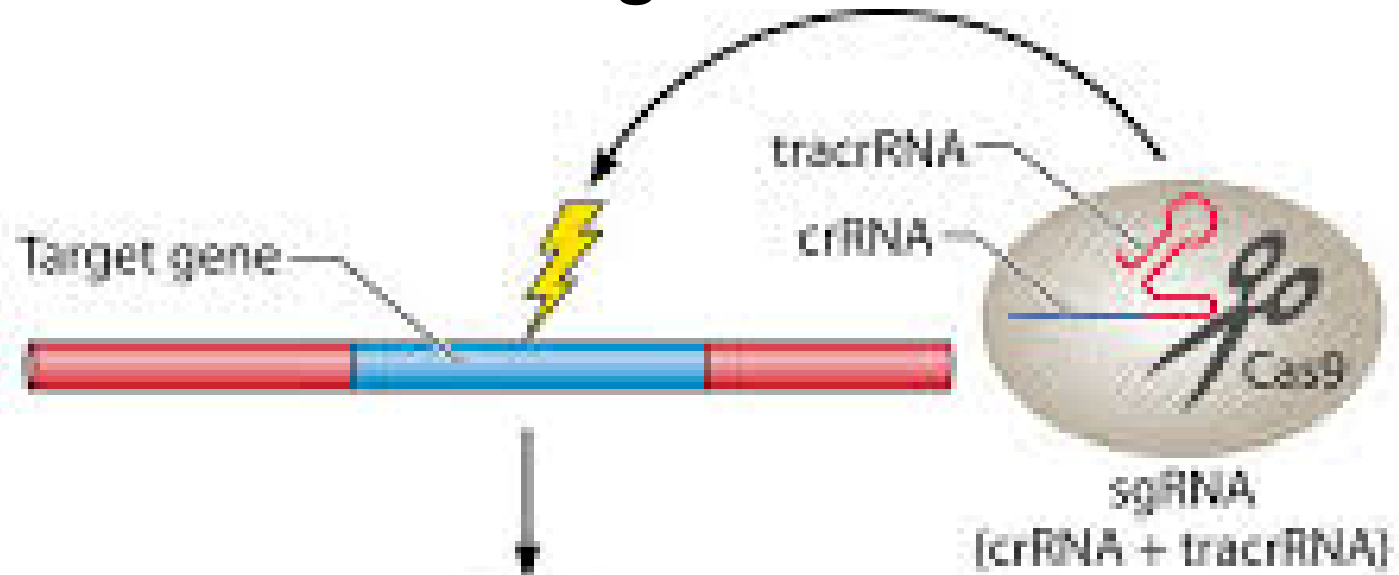
**Interpretation** Short-course oral zidovudine was safe, well tolerated, and decreased mother-to-child transmission of HIV-1 at age 3 months. Substantial efforts will be needed to ensure successful widespread implementation of such a regimen.

# Problems

- Developing countries
- Obligation to ensure access of beneficial treatments for research participants at the conclusion of clinical trials.
- Research with captive populations : prisoners, students, soldiers
- Research with identifiable and targeted communities
- Research with healthy volunteers
- Research with fetuses, embryos, and stem cells
- Research with children
- Research with ethnic and minority populations
- Research involving economically disadvantaged participants

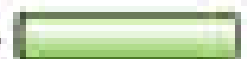
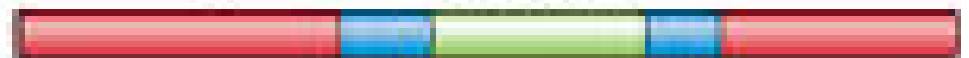
And now...

# Genetics changes?



Deletion

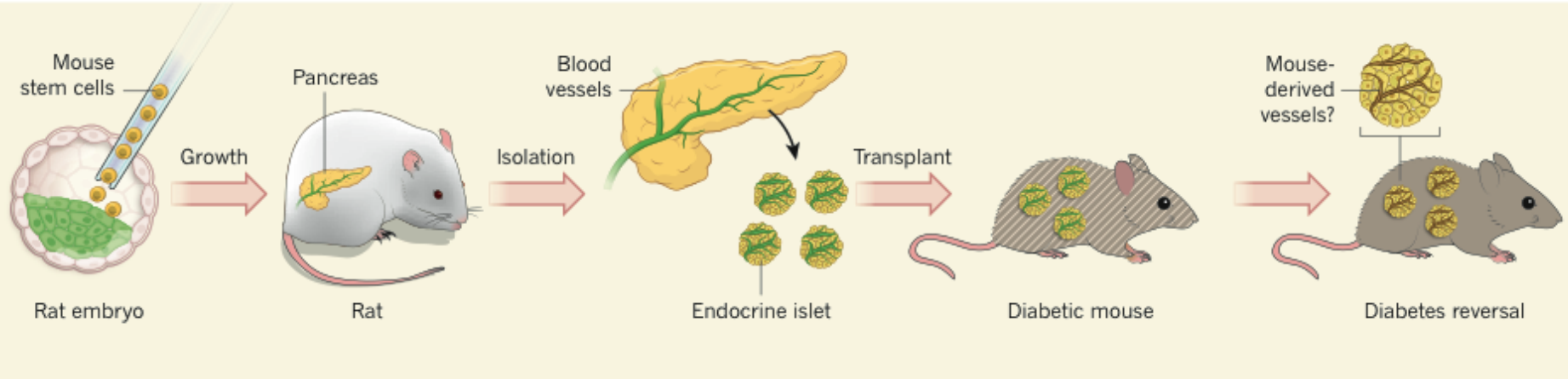
Insertion



CRISP PR cas9

# Interspecies pancreas transplants

A mouse pancreas grown in a rat controls blood-sugar levels when transplanted into a mouse that models type 1 diabetes. This achievement provides a tantalizing glimpse of how organs could be grown for therapeutic use. [SEE ARTICLE P191](#)



## Interspecies organogenesis generates autologous functional islets

Tomoyuki Yamaguchi<sup>1\*</sup>, Hideyuki Sato<sup>1\*</sup>, Megumi Kato-Itoh<sup>1</sup>, Teppei Goto<sup>2</sup>, Hiromasa Hara<sup>2</sup>, Makoto Sanbo<sup>2</sup>, Naoaki Mizuno<sup>1</sup>, Toshihiro Kobayashi<sup>1†</sup>, Ayaka Yanagida<sup>1</sup>, Ayumi Umino<sup>1</sup>, Yasunori Ota<sup>3</sup>, Sanae Hamanaka<sup>1</sup>, Hideki Masaki<sup>1</sup>, Sheikh Tamir Rashid<sup>4,5</sup>, Masumi Hirabayashi<sup>2</sup> & Hiromitsu Nakauchi<sup>1,5</sup>

# HOW TO CREATE A CHIMERA

**1** The gene responsible for making the pancreas is removed from the DNA of a pig embryo



**2** Human stem cells are injected into the embryo



**3** The pig-human embryo is implanted into a sow



**5** After birth the pig would be allowed to grow to adult size - then the human pancreas would be removed for transplant

Test subject: A sow carrying a hybrid embryo

**4** The pig foetus develops as normal - but the human stem cells fill the pancreas void, to create a human organ



Ethics of clinical research is a  
continuous challenge...